DISSERTATION ON

A STUDY ON PREVALENCE OF ASYMPTOMATIC ISCHEMIC HEART DISEASE IN DIABETIC WOMEN AND ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY WITH SILENT MYOCARDIAL ISCHEMIA

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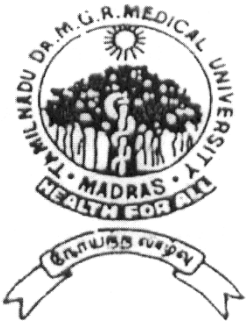

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON THE PREVALENCE OF ASYMPTOMATIC ISCHEMIC HEART DISEASE IN DIABETIC WOMEN AND ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY WITH SILENT MYOCARDICAL ISCHEMIA"** submitted by **Dr. N. VISWANATHAN** appearing for Part II M.D. Branch I General Medicine Degree examination in September 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled "A STUDY ON THE PREVALENCE OF ASYMPTOMATIC ISCHEMIC HEART DISEASE IN DIABETIC WOMEN AND ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY WITH SILENT MYOCARDICAL ISCHEMIA" is done by me at Madras Medical College & Govt. General Hospital, Chennai under the guidance and supervision of Prof. V. Sundaravadivelu, M.D.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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CONTENTS

INTRODUCTION

Patients with diabetes have a 2-4 fold increase in risk of CAD. Better implementation of therapies that reduce cardiovascular risk in diabetic patients will require moving beyond the traditional primary focus on glycaemic control. A working knowledge of the effects of diabetes mellitus on the heart & blood vessels will aid physicians caring for these patients. In general population women experience relative protection from myocardial infarction and usually develop CAD approximately 10 years later than men. However diabetes blunts the cardiovascular benefit of female gender.

In the first national health & nutrition examination survey (NHANES) & the NHANES epidemiologic follow up survey conducted 10 years apart, age adjusted mortality decreased in non-diabetic men & women, less so in diabetic men, but increased by 23% in diabetic women. In the Gruppo Italino per 10 studio della sopravvivenza bell Intarto miocardio – 2 (GISSI – 2) study of thrombolytic therapy in patients with

myocardial infarction, diabetes increased the rate of death in men by 40% and women by 90%.

In the Finnish contribution to the WHO MONICA project (WHO Multinational Monitoring of Trends and Determinate of cardiovascular Disease) 1 year mortality was 38% higher for diabetic men & 86% higher for diabetic women. Silent myocardial ischemia which is common in diabetic patients can be detected by Treadmill test. Though it is said that treadmill false positivity is higher in females, various studies like Guiteras (1972), Linhart (1974), Sketeh (1975), Barolsky (1979), Weiner (1979), Ilsely (1982), Hung (1984), Hlatky (1984), Melin (1985), Robert (1991), Chae (1993), Williams (1994), Marwiek (1995), Morise (1995), shows the average sensitivity in women is 67% and specificity is 67.7%. So in developing nations like India, still tread mill test which is cost effective can be used as a investigation modality for diagnosing CAD in high risk population like diabetic women.

Diabetic Autonomic neuropathy is the most common and troublesome complication of type 2 Diabetes mellitus. Cardiovascular Autonomic neuropathy is a common form of Autonomic neuropathy

causing abnormalities in heart rate control, central and peripheral vascular dynamics. Cardiac autonomic neuropathy has been linked to postural hypotension, exercise tolerance, enhanced intra operative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction and decreased likelihood of survival after myocardial infarction. Hypothesis concerning the multiple etiologies of diabetic neuropathy include metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage and neuro-humoral growth factor deficiency. Cardiac autonomic neuropathy which is considered to be a cause for asymptomatic CAD in diabetics is tested by history and simple bedside tests. Its presence has been correlated with the silent myocardial ischemia.

AIM OF THE STUDY

1. To study the prevalence of asymptomatic ischemic heart disease in diabetic women by exercise stress test.

2. To correlate the presence of cardiac autonomic neuropathy with the asymptomatic ischemic heart disease

REVIEW OF LITERATURE

Diabetes mellitus has become a major threat to human health. Diabetes mellitus is a strong risk factor for the CAD. Eighty percent of the all deaths among diabetic patients are due to atherosclerosis, compared with about 30% among non-diabetes.

Diabetes accelerates the natural course of atherosclerosis in all groups of patients and involves a greater number of coronary vessels with more diffuse atherosclerotic lesions. There is two fold to four fold increase in the relative risk ratio of cardiovascular disease in Type 2 diabetes mellitus compared to general population.[1]

Diabetes in female population

Diabetes is associated with a greater incremental risk in women, completely eliminating the female advantage. The American Heart Association awarded double weight to diabetes in women when calculating IHD risk. More than in men, diabetes dramatically increases the mortality of myocardial infarction in women. T2 DM is associated with obesity, SHT, atherogenic dyslipidemia and insulin resistance all of which have been associated with higher CHD risk. [1]

More so than is men, obesity and body fat distribution appears to be independent CAD risk factors in women. Diabetes is also linked with endothelial dysfunction and a variety of platelet abnormalities. [1]

Although equally likely to have effort angina, women with CHD are more likely than men to experience atypical symptoms such as pain at rest, during sleep (or) with mental stress. These differences make a gender based approach essential in the recognition and assessment of acute and chronic ischemic syndromes. Further non-coronary chest pain syndromes are more common in women, further complicating clinical assessment of chest pain in females. [1]

An overwhelming majority of women and unaware of their cardiovascular risk and physicians do little to educate them. Improvement in prevention of CAD in women requires earlier awareness and identification of risk. Early identification of glucose intolerance, abdominal adiposity and metabolic syndrome, with aggressive behavior modification and immediate weight loss is increasingly recognized as important. [1]

The average lipid profile in women is affected by normal status and changes throughout life. Young women have lower LDL levels and high HDL levels. As women age increases, LDL cholesterol increases,

HDL decreases and the risk of IHD increases. Associated systemic hypertension, smoking, post-menopausal state, obesity, dietary habits and physical inactivity add to the coronary atherosclerotic process. [1]

Coronary atherosclerosis in females:

Estrogen protects premenopausal women from atherosclerosis by producing favorable lipid profile. The differences between men and women in atherosclerosis are not limited to gonodal hormones. Research has shown some fundamental variation in the underlying mechanisms of diseases. [1]

A Japanese study assayed a large population of myocardial infarction patients for the presence of 71 single nucleotide polymorphisms in candidates' gene known to be relevant to the pathophysiology of atherosclerosis. Two were found to be significantly more prevalent in men - connexin 37 and P22 Phix and two different genes were relevant in women plasminogen activator inhibitor-I (PAI-I) and Snomelzia-1 suggesting that the genetic basis underlying among heart disease varies by gender. [1]

Such genetic differences are manifest in the physiology of atherosclerosis, including plaque components (More cellular and fibrous

tissue in women), endothelial function (estrogen induced coronary vasodilatation) and homeostasis (higher fibrinogen factor VII levels in women). [1]

Although coronary thrombosis is overwhelmingly the most common cause of M.I in both genders, women are twice as likely to have plaque erosion (37% in women versus 18% is men). [1]

Non-invasive diagnostic testing in females:

The general principles underlying non-invasive diagnostic testing do not differ in men and women. Resting ECG reveals a higher prevalence of repolarisation (ST-T) wave abnormalities in women with suspected CAD than in men (32% versus 23%).[1]

Treadmill Test:

Treadmill exercise testing is associated with a higher false positive rate and a lower false negative rate than in men (12% versus 40%) suggesting that routine testing reliably excludes the presence of CHD is women with negative tests. Variables that may alter test accuracy are resting ST & T wave abnormalities, peak exercise heart rate, number of diseased vessels, age, drug use (digitalis, diazepam) hyperventilation,

conduction abnormalities, LVH, MVPS, vasospasm and hormonal influences. [1]

In American College of Cardiology/American Heart Association guidelines for exercise testing in asymptomatic persons without known coronary artery disease, Class IIa indication is diabetic patients who plan to start vigorous exercise. [1]

The treadmill protocol should be consistent, with the patient's physical capacity and the purpose of the test. In healthy individuals the standard "Bruce" protocol is popular, and large diagnostic and prognostic data base has been published using this protocol. [1]

The Bruce multistage maximal treadmill protocol has 3 min periods to allow achievement of a steady state before workload is increased. In older individuals (or) those whose exercise capacity is limited by cardiac disease, the protocol can be modified by two 3 minutes warming up stages at 1.7 miles per hour and with 0 percent grade and 1.7Mph and 5% grade. [1]

Exercise physiology during treadmill test:

Cardiac output increases 4-6 folds above basal levels during strenuous exertion in the upright position, depending on genetic

environment and level of training. The maximum heart rate can be estimated from the formula. [1]

MHR = 220 - age in years (with standard deviation of 12 beats/min).

The age predicted maximum heart rate is useful measurement for safety reasons.

In post exercise phase, hemodynamics returns to baselines within minutes of termination of exercise. Vagal reactivation is an important cardiac deceleration mechanism after exercise and the acceleration is well in trained athletes but blunted in patients with chronic heart failure. [1]

The work done during the treadmill test is expressed in metabolic equivalents (MET) which refer to unit of oxygen uptake in a sitting, resting person. One MET is equivalent to 3.5ml O2/kg/min of body wt. [1]

Measured VO2 in Ml O2/min/kg determines number of

ml O2/Kg/min

MET's associated with activity

Work activities can be calculated in multiples of METS. The measurements obtained with cardiopulmonary exercise testing are useful

in understanding an individual patients response to exercise and can be useful in the diagnostic evaluation of a patient with dyspnea. [1]

Types of ST Segment displacement in treadmill:

In normal persons the PR, QRS and QT intervals shorten as heart rate increases - 'P' amplitude increases and the PR segment becomes progressively more down slopping in the inferior leads. [1]

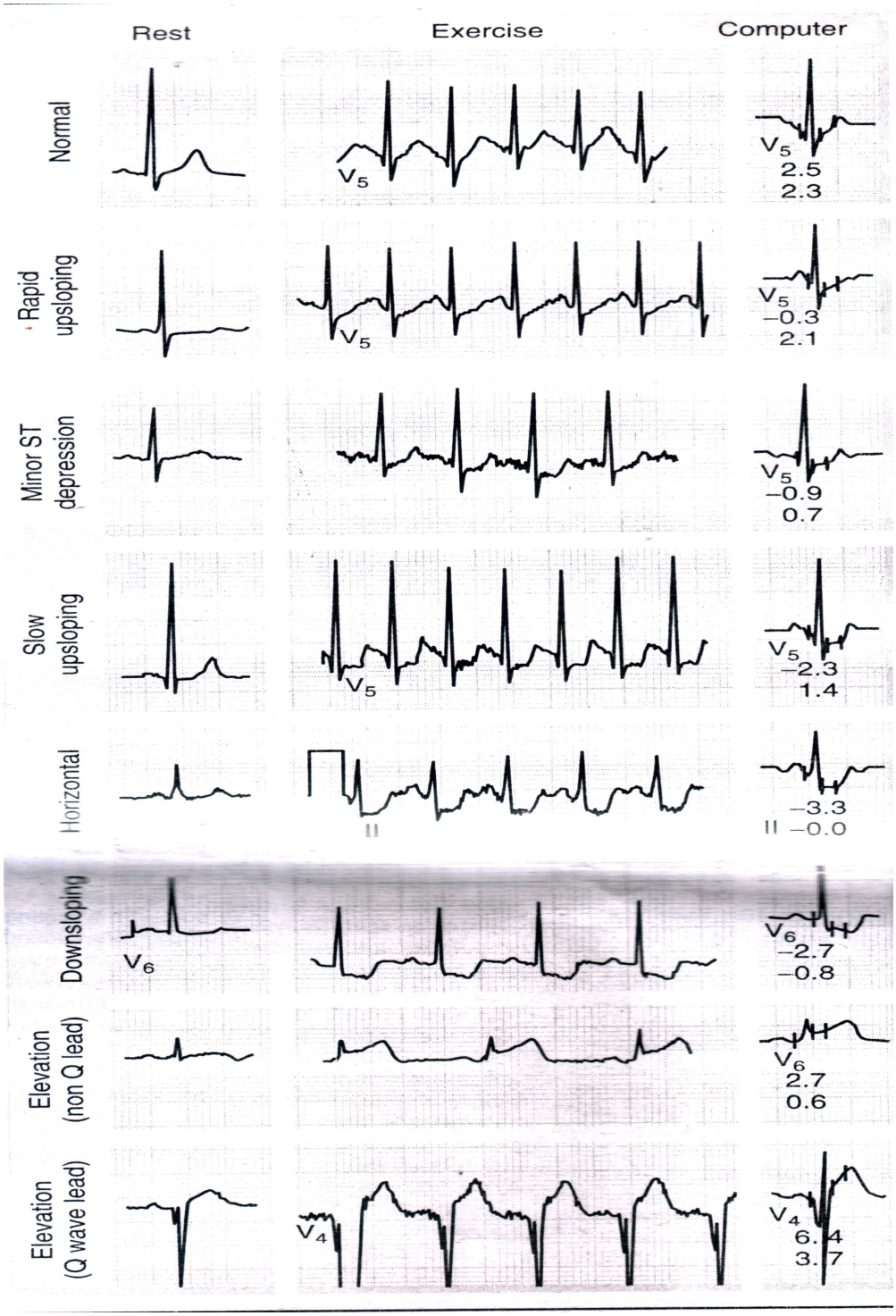
'J' (Junctional) point depression is a normal finding during exercise. In patients with myocardial ischemia, however the ST segment usually becomes more horizontal as the severity of the ischemic response worsens. With progressive exercise the depth of the ST segment depression may increase, involving more ECG leads and the patient may develop angina. [1]

In the immediate post recovery part the ST segment, displacement may persist with down slopping ST segments and 'T' wave inversion, gradually returning to baseline after 5-10 min. In about 10% of patients the ischemic response may appear only in the recovery phase. [1]

The eight different ECG patterns seen during exercise testing.[1]

1. The Normal and rapid upsloping ST segment responses are normal responses to exercise
2. J Point depression with rapid upsloping ST segments is a common response in an older, apparently healthy population.
3. Minor ST depression can occur occasionally at sub maximal workloads in patients with coronary disease; in this illustration, the ST segment is depressed 0.09mV (0.9mm) 80 msec after the J point.
4. The slow upsloping ST segment pattern often demonstrates an ischemic response in patients with known coronary disease or those with a high pretest clinical risk of coronary disease. Criteria for slow upsloping ST segment depression include J point and ST 80 depression of 0.15mV or more and ST segment slope of more than 1.0mV/sec.
5. Classic criteria for myocardial ischemia include horizontal ST segment depression observed when both the J point and ST 80 depression are 0.1 mV or more and ST segment slope is within the range of 1.0mV/sec.

6. Downsloping ST segment depression occurs when the J point and ST 80 depression are 0.1mV and ST segment slope is -1.0mV/sec.
7. ST segment elevation in a non-Q wave noninfarct lead occurs when the J point and ST 60 are 1.0mV or greater and represents a severe ischemic response.
8. ST segment elevation in an infarct territory (Q wave lead) indicates a severe wall motion abnormality and in most cases is not considered an ischemic response.


Rest
Exercise
Computer
Normal
V5
V5
2.5
2.3
Rapid upsloping
V5
V5
−0.3
2.1
Minor ST depression
V5
−0.9
0.7
Slow upsloping
V5
V5
−2.3
1.4
Horizontal
II
−3.3
II −0.0
Downsloping
V6
V6
−2.7
−0.8
Elevation (non Q lead)
V6
2.7
0.6
Elevation (Q wave lead)
V4
V4
6.4
3.7

Non coronary Causes of ST Segment Depression[1]

1.Severe aortic stenosis	9. Glucose Load
2. Severe hypertension	10. Left ventricular hypertrophy
3. Cardiomyopathy	11. Hyperventilation
4. Anemia	12. Mitral valve prolapse
5. Hypokalemia	13. Intraventricular condution disturbance
6. Severe hypoxia	14. Preexcitation syndrome
7. Digitalis use	15. Severe volume overload (aortic, mitral regurgitation)
8.Sudden excessive exercise	16. Supraventricular tachyarrhythmias

Exercise Parameters Associated with an Adverse Prognosis and Multivessel Coronary Artery Disease. [1]

1.Duration of Symptom-limiting exercise <5METs
2.Failure to increase systolic blood pressure $\geq$ 120mm Hg, or a sustained decrease $\geq$ 10mm Hg, or below rest levels, during progressive execise.
3.ST segment depression $\geq$ 2mm, downsloping ST segment, starting at <5 METs, involving $\geq$ 5 min into recovery.
4.Exercise-induced ST segment elevation (a V excluded)

5.Angina pectoris at low exercise workloads
6.Reproducible sustained (>30sec) or symptomatic ventricular tachycardia
7.Acute systemic illness (pulmonary embolism, aortic dissection)s

Measurement of ST segment displacement:

For purpose of interpretation, the PQ junction is usually chosen as the iso electric point. The TP segment represents a true iso electric point but is an impractical choice for most routine clinical measurements. The development of 0.1 mV (or) greater of 'J' point depression measurement from the PQ junction with a relatively flat ST segment slope (e.g.) <0.7 to 1MV/sec), depressed 0.10 MV (or) more 80 m.sec after the 'J' point (ST 80) in three consecutive beats with a stable baseline is considered to be an abnormal response. [1]

When the ST 80 measurement is difficult to determine at rapid heart rate (>130 beats/min) the, ST 60 measurement should be used. The ST segment at rest may occasionally be depressed. When this occurring the 'J' point and ST 60 (or) ST 80 measurements should be depressed an additional 0.1 MV (or) greater to be considered abnormal. [1]

When the degree of resting St depression is 0.1 MV (or) greater, the exercise ECG becomes less specific and myocardial imaging modalities should be considered. [1]

Exercise induced ST segment depression does not localize the site of myocardial ischemia nor does it provide a clue about which coronary artery involved. But exercise induced ST segment elevation is relatively specific for the territory of myocardial ischemia and coronary artery involved. [1]

Mechanism of ST segment depression

Dynamic changes in coronary artery at the site of an atherosclerotic plaque may result in diminished coronary flow during static (or) dynamic exercise, instead of the expected that normally occur from coronary vasodilatation in a normal vessel; that is perfusion present distal to the stenotic plaque actually falls as during exercise, resulting in reduced subendocardial blood flow. Thus regional left ventricular myocardial ischemia may result not only from an increase in myocardial O2 demand during exercise but also from a limitation of coronary flow as a result of coronary vasoconstriction (or) inability of vessels to sufficiently vasodilate at (or) near the site of an atherosclerotic plaque. [1]

In normal persons, the action potential duration of the endocardial region is longer than that of the epicardial region and ventricular repolarisation is from epicardium to endocardium. The action potential duration is shortened in the presence of myocardial ischemia and electrical gradients are created, resulting in ST segment depression (or) elevation depending on the surface ECG leads. At the molecular level, activation of sarcolemmal ATP - sensitive potassium channels by ischemic ATP depletion may play a role. [1]

Non electrocardiographic observation in treadmill

Blood Pressure

The normal exercise response is to increase systolic BP progressively with increasing work loads to a peak response ranging from 160-200 mmHg with the higher range of the scale in older patients with less compliant vascular system. In asymptomatic normotensive individuals an exaggerated exercise systolic and diastolic BP response during exercise (or) exaggerated peak systolic BP to 214 mmHg (or) greater (or) an elevated systolic (or) diastolic BP at the 3rd minute of recovery is associated with significant increased long term risk of hypertension. [1]

Cardiac autonomic neuropathy (CAN)

CAN probably contribute to the poor prognosis of CHD and CHF in diabetes. The majority of patients with CAN come to clinical attention with complaints of postural hypotension, resting tachycardia, exercise intolerance (or) prior myocardial ischemia (or) infarction. The risk for CAN depends on the duration of diabetes and the degree of glycaemic control and leads to parallel the development of other end organ disease related to diabetes such as retinopathy, nephropathy and vasculopathy. Symptoms and signs of CAN often occur relatively late in the natural history of this complication. [1]

Simple bed side tests for cardiac autonomic neuropathy diagnosis: [2]

	Normal	**Abnormal**
Heart-rate variation during deep breathing (Maximum-minimum (bpm)	>15	<10
Heart-rate increase on standing (15s after standing (bpm))	>15	<12
30^{th} beat:15^{th} beat ratio (RR interval)	>1.04	<1.00
Heart-rate change during Valsava Maximum: minimum ratio	>1.21	<1.20
Postural fall in systolic BP 2 min after standing (mmHg)	<10	>20

Prevalence of Cardiac autonomic neuropathy (CAN) [1]

The reported prevalence of CAN varies with the population studied and methods used. Regarding of these variations CAN appears to be common in diabetes. A summary of 15 reports on CAN suggests that the prevalence is in between 2.6 and 90% in diabetic population. The average incidence is about 30%.

Pathology of Autonomic neuropathy in Diabetes: [7]

Pathologic changes in the autonomic nervous syndrome were studied postmortem in many diabetic cases. All had clinical evidence of peripheral sensory motor neuropathy and developed disturbances of autonomic function that included postural hypotension, diarrhea, bladder dysfunction and signs of cardiac denervation. In celiac and other sympathetic ganglia there were many distended (Giant) or vacuolated nervous as well as enlarged club shaped neural processes. The vagus nerve and sympathetic trunks showed severe loss of myelinated fibers. [7]

There were inflammatory changes in autonomic ganglia in all cases and in (or) around bundles of unmyelinated nerve fibers in many. These findings suggest that there may be several different pathogenetic

mechanisms involved in the development of autonomic neuropathy in diabetes. [7]

Diabetic patients have a high rate of coronary heart disease, which may be asymptomatic owing to autonomic neuropathy. Silent ischemia is significantly more frequent in patients with autonomic neuropathy than in those without autonomic neuropathy (38% versus 5%).[4]

It is clear however that a reduced appreciation of ischemic pain can impair timely recognition of myocardial ischemia (or) infarction and there by delay appropriate therapy. [4]

In non-diabetic patients, acute myocardial infarction has a circadian variation with a significant morning peak. The characteristic diurnal variation in the occurrence of myocardial infarction is altered in diabetic patients with a lower morning peak and higher percentage of infarction during evening hours. The blunted morning surge of incidence of myocardial infarction results from altered sympatho-vagal balance in patients with cardiac autonomic neuropathy. Mortality rates after a myocardial infarction are also higher for diabetic patients than for non-diabetic patients. This may be due to autonomic insufficiency, increasing the tendency for development of ventricular arrhythmia and cardiovascular events after infarction.[4]

Autonomic manifestations

Abnormal autonomic function tests are often found in patients with clinical features of sensory neuropathy, and almost any aspect of autonomic function can be affected. However, symptoms of autonomic neuropathy are unusual and are commonest in patients with poorly controlled type I diabetes. In all of the autonomic syndromes described below, symptoms may be chronic or strikingly intermittent. [2]

Most longitudinal studies point to a common sequence of autonomic involvement in patients with diabetic autonomic neuropathy. In the cardiovascular system, the earliest abnormality detected by systematic and sensitive testing is a decrease in heart- rate variability during deep breathing, followed by alterations in the heart rate on standing and then the Valsalva maneuver. Postural hypotension is a relatively late event. This progression suggests that parasympathetic (vagal) fibers are damaged first, followed by the sympathetic outflow. Abnormal autonomic function tests are much more common than significant autonomic symptoms. [2]

Symptomatic, but not asymptomatic, autonomic neuropathy has been associated with a poor prognosis. But there is dispute as to whether

this is related to the neuropathy itself or to coexistent macrovascular disease or other complications. [2]

Abnormal sweating

This is one of the commonest, but frequently neglected, symptoms of diabetic autonomic neuropathy. Gustatory sweating, precipitated by eating cheese and other foods, is characteristic. Sweating is often profuse over the face and sometimes upper chest, corresponding to the area supplied by the superior cervical ganglion. Some patients find this socially debilitating.

Other abnormalities of sweating include the dry neuropathic foot, which allows cracking of the skin and the entry of infection, and episodic nocturnal sweating that cannot be attributed to hypoglycaemia. [2]

Cardiovascular changes

These include abnormalities of the cardiovascular reflexes related to changes in posture and respiration, with severe postural hypotension in extreme cases. [2]

Postural hypotension

This is due to the impairment of the increase in cardiac output and of the sympathetically mediated vasoconstrictor response in the lower limbs, which normally follow standing upright. In diabetic neuropathy, this is a common manifestation of sympathetic denervation. It can be exacerbated by administration of insulin (which acts as a vasodilator at pharmacological concentrations) and of diuretics, antihypertensives and tricyclic antidepressants (which also have vasodilator activity). On standing, blood pressure is normally maintained, may rise slightly or may fall, but the systolic drop does not usually exceed 10 mmHg; a significant drop is generally taken as > 20 mmHg, although the magnitude of the systolic fall on standing does not correlate tightly with symptoms of dizziness. [2]

Postural hypotension is often worse on getting out of bed in the morning, but often varies substantially with time. The diagnosis is made simply by measuring the blood pressure with the patient lying and then standing for up to 2 min (some patients show a delayed fall).[2]

Athero thrombotic disease

Atheroma develops earlier and faster in diabetes, leading to widespread lesions throughout the arterial tree, including the smaller arteries. Thickening of the intima is an early change. Hyaline degeneration and thickening of the muscular media may contribute to hypertension and often undergoes calcification (medial sclerosis). An important functional abnormality is impaired arterial relaxation, due to failure of the endothelium to produce nitric oxide (NO), a potent vasodilator. Procoagulant changes on the endothelial surface promote adhesion of macrophages (the precursors of foam cells of the atheromatous plaque) and platelets, favoring thrombosis. Platelet-rich thrombus in the coronary arteries is unstable and likely to rupture, causing acute coronary occlusion. [2]

Atherogenic risk factors like hyperglycemia, hypertension, dyslipidemia and central obesity cluster together with insulin resistance in the ‘metabolic’ syndrome (syndrome X), which is strongly associated with accelerated atheroma formation and cardiovascular disease. The presence of diabetes amplifies the effect of other coexisting risk factors. Disorders of coagulation and fibrinolysis are also associated with

syndrome X and probably contribute to atherothrombotic disease. Clustering of these factors is unexplained. [2]

Cardiovascular risk rises as blood glucose increases above subdiabetic levels. The relationship may be J-shaped. In diabetic people, tight glycaemic control has not yet been shown to reduce macrovascular events, except of metformin treatment, which significantly decreased fatal myocardial infarction rate in type 2 diabetic patients. Other actions of metformin (reducing pressure and obesity) may be responsible. [2]

Hyperglycemia leads to advanced glycation end-products (AGE) formation in the arterial wall, damaging structural proteins and generating toxic reactive oxygen species. Sequelae include increased endothelial permeability, impaired NO-mediated vasorelaxation, upregulation of procoagulant and adhesion proteins on the endothelium, and attraction of macrophages that form foam cells. AGEs interact with specific receptors (RAGEs) on endothelial and other cells to cause specific effects. Genetic polymorphisms of the RAGE gene may modulate production of inflammatory mediators in arteries. Insulin stimulates vascular smooth muscle cell proliferation and production of the fibrinolysis inhibitor, plasminogen activator inhibitor (PAI). High insulin levels in insulin resistant states may therefore be atherogenic. Other commonly associated

risk factors are hypertension (30-45% of diabetic people), dyslipidemia (typically raised low density lipoproteins, dominated by highly atherogenic small dense low-density lipoprotein, low high-density lipoproteins, raised triglycerides) and obesity, an independent risk factor.[2]

Clinical syndromes and management

Myocardial ischemia may present atypically or without pain, and 'silent' ischemia carries a worse prognosis than in non-diabetic people. Vascular disease in the legs and cerebral circulation commonly coexist and are two to three times more frequent than in the general population. Early and extensive investigation (including invasive test such as coronary angiography) may therefore be needed in patients with few symptoms. [2]

Primary preventative measures includes weight loss if obese, regular physical activity and smoking cessation; optimizing glycaemic control, using metformin in obese type 2 patients; correcting dyslipidemia and hypertension; and aspirin (75mg/day). Target cholesterol concentration is <4.8 mmol/L, and blood pressure should be <135/85 mmHg. [2]

Beta blockers and angiotensin-converting enzyme (ACE) inhibitors are useful in treating angina and hypertension and also have cardio-

protective effects in diabetic patients. ACE inhibitors also slow the progression of nephropathy, and some calcium-channel antagonists decrease the risk of infarction in diabetic people. Heart failure is treated conventionally with ACE inhibitors and diuretics; certain beta blockers (e.g. carvedilol) may also be useful. [2]

Unstable angina carries a 50% higher risk of progression to myocardial infarction than in non-diabetic subjects, and requires intensive treatment with low molecular-weight heparin and a beta blocker; addition of either clopidogrel or a platelet glycoprotein IIb/IIIa inhibitor (e.g. tirofiban), to block platelet aggregation, further reduces risk of infarction or death. Urgent coronary revascularization is indicated if medical measures fail. [2]

Acute myocardial infarction should be treated with immediate thrombolysis (even in the presence of retinopathy), aspirin and a cardioselective beta-blocker. An ACE inhibitor should be given early unless contraindicated. Blood glucose should be tightly controlled in all diabetic patients, according to the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) protocol, insulin/glucose solution infused intravenously to maintain levels of 7-11 mmol/L for at least 24h, followed by intensive subcutaneous insulin

treatment for at least 3 months. Insulin given in this way may reduce myocardial damage from non-esterified fatty acids and block excessive neuroendocrine activation. [2]

Coronary revascularization relieves symptoms as effectively in diabetic as in non-diabetic people, although long-term survival is lower. Percutaneous transluminal coronary angioplasty (PTCA) with stenting (and probably a platelet inhibitor) is preferred for accessible lesions in larger vessels. Coronary artery bypass grafting (CABG) is generally reserved for difficult or multiple occlusions and for re-stenosis after angioplasty.[2]

Dyslipidemia in T2 D M

Lipid metabolism is commonly deranged by the diabetes mellitus, often with additional contributions from coexistent renal or hepatic disorders. These lipid alterations play an important role in the development of atherosclerosis, and contribute to the instability of atheromatous plaques. Gross hypercholesterolemia is not a feature of diabetic dyslipidemia, but at any given level of cholesterol, a diabetic subject has two to three times the cardiovascular risk of non- diabetic. [2]

Lipid abnormalities associated with type I diabetes are largely related to the level of glycaemic control. Hyperglycemia is associated with raised low-density lipoprotein (LDL) cholesterol and triglyceride concentrations and low HDL-cholesterol, abnormalities which are reversed by normalizing glycaemia. [2]

The pattern of dyslipidemia in type 2 diabetes is that characteristically seen in the insulin-resistant states and the metabolic syndrome. Low HDL and raised triglyceride concentrations are accompanied by normal LDL-cholesterol levels, although this is likely to be dominated by highly atherogenic small dense LDL particles. Non-diabetic but insulin resistant first degree relatives of type 2 diabetic subjects share this atherogenic profile, suggesting that it precedes the development of clinical diabetes. [2]

Systemic hypertension

Hypertension commonly coexists with type 1 and type 2 diabetes and is particularly associated with diabetic nephropathy. In its own right, it is a major risk factor for both myocardial infarction and stroke. In the UKPDS, 32°/o of type 2 diabetic males and 45°/o of females with no clinical evidence of atheromatous disease were hypertensive (according to the World Health Organization criteria of systolic pressure> 160

mmHg, and/or diastolic > 90 mmHg) or were taking antihypertensive drugs. In male subjects who already had coronary-artery disease, the prevalence of hypertension was even higher at 46%.[2]

Hypertension is an important feature of the cluster of cardiovascular risk factors termed the metabolic syndrome. The links between these factors remain largely unexplained. The characteristic dyslipidemia of insulin resistance may contribute to hypertension, as small dense LDL particles are especially susceptible to oxidation, and oxidized LDL can suppress endothelial NO production and so promote vasoconstriction; hypertriglyceridemia also impairs endothelium-dependent vasorelaxation. A role of dyslipidemia is supported by studies showing that fibrates used to treat hypercholesterolaemia also reduced the prevalence of hypertension by up to 25%.[2]

Obesity

Obesity predisposes to type 2 diabetes, and to hypertension, dyslipidaemia and ultimately atheroma - one of the major causes of premature death in the obese. Indeed, obesity is now recognized as a cardiovascular risk factor in its own right. [2]

Truncal or male-pattern obesity, with excess fat deposited both subcutaneously around the abdomen and within the visceral cavity is

particularly associated with type 2 diabetes and the other components of the metabolic syndrome. For unknown reasons, truncal obesity is associated with insulin resistance and proinflammatory responses that cause glucose intolerance and a highly atherogenic risk profile. Candidate mediators produced by adipose tissue that may contribute include NEFAs and cytokines such as TNF-alpha. Reduced levels of adiponectin, an insulin sensitizing protein whose secretion by adipose tissue is paradoxically decreased in obesity, may also contribute to both insulin resistance and atherogenesis. The thiazolidinediones ameliorate some of these adverse effects of adipose tissue (e.g. lowering NEFA levels), raising the prospect that these agents may reduce cardiovascular risk in type 2 diabetes. [2]

Haemostasis in diabetes

Diabetes is associated with a variety of abnormalities in coagulation, fibrinolysis and platelet function. These include increases in specific procoagulant proteins - factor VIII , vWF, factorVII , factor X and fibrinogen together with potentially prothrombotic decreases in the coagulation inhibitors, protein and antithrombin III. Some of these disturbances differ quantitatively between type 1 and type 2 diabetes, and

some show particularly strong associations with atherothrombotic disease and with microvascular complications, especially nephropathy. [2]

Cardiovascular autonomic neuropathy and increased cardiovascular morbidity and mortality in diabetes mellitus possible mechanisms[1]

1. Impaired angina recognition Silent ischemia and infarction.

2. Decreased threshold for ischemia

Increased resting heart rate and blunted chronotropic response to exercise,

Impaired coronary vasomotor regulation.

3. Prolonged QT interval

Increased lethal arrhythmias and sudden death (with or without myocardial ischemia)

4. Abnormal diastolic and systolic function

Contributes to diabetic cardiomyopathy. Increased cardiac mass

Adversely affects the natural history of congestive heart failure

5. Increased peri-operative risk

Increased need for hemodynamic support

Reduced hypoxia-induced respiratory drive .

6. Alteration of normal circadian variation of sympatho-vagal activity

Lack of normal nighttime decrease in blood pressure

Loss of night time protection against myocardial infarction

7. Increased prevalence of other cardiovascular risk factors and other Complications

Increased microvascular complication

Increased rate of progression of glomerolopathy

Increased prevalence of hypertension and dyslipidemias[1]

PHARMACOLOGIC MANAGEMENT FOR CONTROL DIABETES[3]

Sulfonylureas:

Sulfonylureas are the typical therapy for lean patients with type 2 disabetes and are used in combinations with other agents in obese type 2 patients. Sulfonylureas bind to a receptor on the beta cells and inhibit the sodium-adenosine triphosphate (Na-ATP) channel; an increase in intracellular calcium results in insulin exocytosis.

Some experts point to a possible risk of increased myocardial damage in patients with known CAD who use sulfonylureas at the time

of an ischemic event. Prevention of protective ischemic preconditioning of the heart by inhibition of the potassium (K)-ATP channel is the putative mechanism. The UKPDS data do not support this concern. The authors agree and use sulfonylureas in appropriate patients with CAD. [3]

Repaglinide:

This newer insulin secretagogue binds to a different receptor site than do the sulfonylureas on the K-ATP channel. The half-life of this agent is 3.7 h, which makes it effective for postprandial rather than preprandial hyperglycemia, for use in the elderly and for diabetic patients with chronic renal failure. [3]

Metformin:

Metformin is a biguanide drug that has been in use in Europe for over 30 years and was approved in the United States in 1995. The main mode of action of metformin is decreasing hepatic glucose output primarily by inhibiting gluconeogenesis, typically without hypoglycemia.

Metformin is effective alone or in combination with insulin, sufonylureas, and thiazolidinediones. The drug usually results in weight loss as a result of decreased appetite for up to 1 year after the inititation of therapy.

Significant decrease in LDL cholesterol and triglycerides occur. The incidence of lactic acidosis with metformin is 9 per 100,000 person-years. Contraindications to its use include an elevated creatinine level (>1.4 in women, <1.5 in men), congestive heart failure, severe pulmonary disease, or any hypoxic state. [3]

Thiazolidinediones:

Thiazolidinediones promote insulin-stimulated glucose transport in muscles and adipocytes through a mechanism of action involving actuating peroxisome proliferators activated receptor-gamma (PPAR-γ) ligands. Binding to the nuclear receptor promotes differentiation of adipocytes and increased expression of glucose transporter.Thiazolidinediones has been shown to be effective both as monotherapy and in combination with insulin, sulfonylureas, and metformin. [3]

Endogenous C peptide is necessary for all the thiazolidinediones to be effective when used in combination with insulin. These agents can result in a reduction from two injections of insulin a day to one. Triglyceride levels can be lowered with troglitazone. There is a small increase in the plasma LDL concentration, along with a favorable increase in the ratio of buoyant LDL to the more antherogenic small dense LDL. The thiazolidinediones are associated with weight gain partly resulting from improvement in glycemic control. With troglitazone, monitoring of liver function should be done monthly for the first year and quarterly thereafter. [3]

Troglitazone has resulted in fulminate hepatic failure in about 1 in 60,000 patients on the medication; this is felt to be an idiosyncratic reaction. Patients with a history of liver disease, possibly including hepatitis C (depending on severity), and those who ingest more than a moderate amount of alcohol should not be started on this agent. Because of the potential for liver disease, troglitazone has been removed from use by the FDA. [3]

Two other drugs in this class were approved by the U.S. Food and Drug Administration (FDA) in mid-1999, and the data to date support

equal efficacy with less hepatotoxicity. No head – to- head studies of these agents are available. Monitoring of liver function tests with rosiglitazone and pioglitazone is recommended every 2 months for the first year and periodically thereafter, since it has not been determined that serious liver events with troglitazone are a class effect of the thiazolidinediones or are specific to troglitazone. [3]

Rosiglitazone monotherapy results in a decrease of Hb A1c of 0.8 to 1.5 percent greater than that seen with placebo, with the greatest reduction seen when it was given in two divided doses. Combination studies of rosiglitazone with metformin for 26 weeks resulted in a 1.0 to 1.2 percent placebo-adjusted decrease in HbA1c. Although rosiglitazone is currently approved for use as monotherapy and in combination therapy with metformin, it also is expected to be efficacious with sulfonylureas or insulin. Rosiglitazone has been reported to result in an increase in LDL and HDL cholesterol concentrations between 12 and 19 percent, with changes in serum triglycerides similar to those seen with placebo. [3]

Pioglitazone, the newest thiazolidinedione, has been approved for use as monotherapy and in combination with metformins, sulfonylureas, and insulin. In three randomized, double-blind placebo controlled trials

of 16to26 weeks duration, changes in HbAlc were 1.0 to 1.4 percent. Increases in

alanine aminotransferase (ALT) occurred in 0.26 percent of treated patients, a result that was not different from that with placebo. Patients treated with pioglitazone showed a decrease in serum triglyceride (9.3 to 9.6 percent), increases in HDL (12.2 to 19.1 percent), and increases in LDL (5.2 to 6.0 percent) with the 30-45-mg doses, respectively. [3]

Alpha-Glucosidase Inhibitors:

Acarbose and miglitol work in the intestine to reversibly inhibit brush border alpha-glucosidases, resulting in a delay in carbohydrate absorption. Only about I percent of the drug is absorbed from the gastrointestinal tract. These drugs cause a 30 percent decrease in postprandial glucose in contrast to a 10 percent decrease in fasting glucose levels. They are adjuncts to other oral agents and rarely are potent enough to be used as mono therapy. [3]

Insulin:

The natural history of type 2 diabetes is one of progressive beta-cell failure. Therefore, after approximately 10 years of the use of oral hypoglycemic agents, insulin will be required in combination with oral agents as the sole therapy. Although endogenous hyperinsulinemia is clearly associated with atherogenesis, there is no compelling evidence of increased risk of cardiovascular disease or increased mortality from exogenous insulin therapy. [3]

MATERIALS AND METHODS

PLACE OF STUDY

Institute of internal medicine

Madras medical college & Government general hospital

Chennai 03

INCLUSION CRITERIA

1. Known diabetic women on treatment (OHA & insulin therapy)
2. Diabetic women not on treatment for CAD
3. Patients not on beta blockers
4. Duration of diabetes within 10 years
5. Echocardiography normal

EXCLUSION CRITERIA

1. Patients with peripheral vascular disease as evidenced by absent peripheral pulses
2. Type 1 diabetes mellitus
3. Known case of coronary artery disease
4. Signs of left ventricular failure

5. Uncontrolled systemic hypertension
6. High risk unstable angina
7. Age > 65 yrs
8. Other absolute contraindications for exercise stress test

STUDY POPULATION

Of the 107 patients enrolled for the study who attended out patient clinic of institute of internal medicine, Government General Hospital, 30 patients were selected for the treadmill test and presence of cardiac autonomic neuropathy in them was tested by history and simple bed side tests. Other 77 patients are excluded as per exclusion criteria.

These groups of patients were investigated in dept of cardiology Govt. Gen Hospital and other appropriate investigations are done in biochemistry lab attached to op department, Govt. Gen Hospital. Autonomic neuropathy testing by simple bet side test was done in op department using ECG monitor and BP apparatus for the same 30 patients.

Tread mill test was performed for these 30 patients using standard Bruce protocol.

STUDY DESIGN

The presence of Cardiac autonomic neuropathy was correlated with the associated asymptomatic ischemic heart disease. Asymptomatic ischemic heart disease patients are those who are positive for inducible ischemia in TMT but without having angina at rest.

LAB METHODS

In the study population fasting plasma glucose was measured using glucose oxidase & pyruvate oxidase methods from over night fasting sample and results were read by calorimeter. With the same method postprandial blood sugar was measured 2 hrs after the breakfast.

BODY MASS INDEX

Body mass Index was calculated using the formula

BMI = Weight (in Kg) / Height in metre^2

In the study population, Body mass index of <25, 25 to 30 and >30 are divided into three groups. TMT positivity in these groups was analyzed.

CARDIAC AUTONOMIC NEUROPATHY

Cardiac Autonomic neuropathy was tested by

1. **Heart rate response to deep breathing.**

Deep breathing is defined as 6 breaths per minute with 5 seconds of inspiration & 5 seconds of expiration, the maximum and minimum heart rate is measured.

2. Heart rate increase15 sec after standing using E C G monitor

3**. Drop in systolic blood pressure 2 minutes after standing**

Cardiac autonomic neuropathy is said to be positive when heart rate variation to deep breathing is less than 10, heart rate increase 15 seconds after standing is less than 12 and drop in systolic BP 2 minutes after standing is more than 20 mmHg.

Though other tests like ratio of RR interval between 30 and 15 beat after standing and heart rate change during valsalva maneuver are available, due to simplicity, practical difficulty and patients acceptance these tests are omitted .***In various international studies positivity of 2 out of 5 bed side tests was taken as cardiac autonomic neuropathy positive***. ***In our study positivity of 3 bed side tests are considered as positive for CAN.*** Apart from the tests cardiac autonomic imbalance was

also tested by detailed history. In the history symptoms suggestive of **orthostatic intolerance**[8] like

H/o light headedness

H/o weakness or tiredness

H/o cognitive difficulty (thinking /concentrating)

H/o vertigo

H/o anxiety

H/o palpitations

H/o sweating abnormality

H/o diarrhea

H/o constipation

Since cardiac autonomic neuropathy is usually associated with other features of autonomic neuropathy this questioner was useful in assessing the patients along with the bed side tests.

TREAD MILL TEST:

Techniques

1. The standard Bruce protocol was used since large diagnostic and prognostic data base has been published using this protocol. The Bruce

multistage maximal treadmill protocol has 3 minutes periods to allow achievement of steady state before work load is increased.

2. Patients were instructed not to eat drink caffeinated beverages for 3 hours before testing and to wear comfortable shoes and loose fitting cloths.

3. Unusual physical exertion was avoided before testing.

4. Patients were advised about the risks and benefits of the procedure.

5. A written informed consent form was obtained.

6. Adequate skin preparation was done to obtain high quality recordings.

7. The areas of electrode application are rubbed with an alcohol pad to remove oil & rubbed with free sand paper and a rough material to reduce to skin resistance to 5000 ohms.

8. Cables connecting the electrodes and recorders were light flexible and properly shielded.

9. Room temperature was adjusted between 64 and 72˚f (18 & 22˚ c) and humidity less than 60%.

10. Tread mill walking was demonstrated to the patients.

11. The heart rate, blood Pressure and ECG were recorded at the end of each stage of exercise. Immediately before & immediately after stopping exercise, at the onset of an ischemic response and for each minute for at least 5-10 minutes in the recovery phase.

12. A minimum of three leads were display continuously on the monitor during the test.

13. Patients were at the sitting position immediately after the exertion.

14. The supine position was avoided because it increases end diastolic volume and has the potential to augment ST segment changes.

TMT RESULTS INTERPRETATION

Normal persons

In normal persons, PR, QRS and QT intervals shorten as the heart rate increases. P amplitude increases and PR segment becomes progressively more downsloping in the inferior leads. J point or junctional depression is the normal finding during exercise.

Abnormal response

The development of 0.1 mV (1 mm) or greater of J point depression measured from the PQ junction with a relatively flat ST

segment slope, depressed 0.1 mV or more 80 m.sec after the J point (ST 80) in 3 consecutive beats with a stable baseline is considered to be an abnormal response. When the ST 80 measurement is difficult, to determine at rapid heart rate (>130 beats/min), ST 60 measurement is used.

In our study

1. ST segment depression of > =1mm during exercise and early recovery period was considered to be TMT positive for inducible ischemia.
2. Development of classical angina during the test is considered to be strongly positive response.

Workload

Workdone during the exercise stress test is expressed in MET (Metabolic equivalents). 1 MET = 3.5 ml/O2/min/Kg of body weight.

Exercise time

Exercise time is calculated in minutes. Each stage is consisted of 3 minutes

Hypertension

Hypertensive response during treadmill was considered when systolic BP raised more than 214 mmHg. These types of patients are more prone to develop hypertension in the future.

The TMT was terminated if the patient developed any of the following features.

1. Drop in systolic blood pressure despite an increase in workload
2. When accompanied by other evidence of ischemia
3. Moderate to severe angina (grade ¾)
4. Increasing nervous system symptoms (e.g., ataxia, dizziness or near-syncope)
5. Signs of poor perfusion (cyanosis or pallor)
6. Technical difficulties in monitoring ECG or systolic blood pressure
7. Subject's desire to stop
8. Sustained ventricular tachycardia
9. ST elevation (≥1.0mm) in non infarct leads without diagnostic Q waves (other than V1 or aVL)
10. Fatigue, shortness of breath, wheezing, leg cramps, or claudication
11. Development of bundle branch block of intra ventricular conduction delay that cannot be distinguished from ventricular tachycardia
12. Hypertensive response

STATISTICAL ANALYSIS

Statistical analysis was carried for 30 subjects after categorizing each variable. Autonomic neuropathy bedside tests are performed for all the patients. Age, duration of diabetes, BMI, systemic hypertension, menopause and percentage of CAN positivity in TMT positive and negative group were analyzed. The significance of difference in mean between means were calculated using z test and difference in proportions using chi-square statistic.

Statistical significance is taken when $P < 0.05$. Statistical analysis was carried out using standard formulae. Microsoft excel 2003 and SPSS (statistical package for social sciences) version 13.0 softwares were used for data entry and analysis.

OBSERVATIONS

We included 30 diabetic women for the study and all of them underwent treadmill test. Treadmill test was done by standard Bruce protocol.

Table.1 Prevalence of asymptomatic IHD in female diabetics

Total number of patients in whom TMT was done	TMT positive	Percentage
30	9	30%

Table.2 Patient characteristics

	TMT Positive group	TMT Negative group	P value
Number	9	19	
Age	49.78 ± 8.11	45.21 ± 7.66	0.16
BMI	27.39 ± 3.91	27.01 ± 4.10	0.84
Mean duration of diabetes	5.78 ± 3.31	4.32 ± 2.81	0.27
% of autonomic neuropathy positivity	77.78%	10.52%	<0.001
SHT	55.55%	42.1%	0.48
Menopause	22.22%	15.78%	0.69

Table.3 TMT parameters in patients

	TMT positive	TMT negative	P value
Exercise time	5.51 ± 1.91	7.43 ± 2.19	0.016
Workload in METs	8.81 ± 2.28	10.59 ± 2.71	0.06
% Predicted maximum HR	91.5 ± 9.71	90.71 ± 10.14	0.12

Table.4 CAN predictors in patients

	TMT positive	TMT negative	P value
HR variation to deep breathing	11.67 ± 7.45	20.16 ± 5.41	0.0027
HR increase 15 seconds after standing	12.22 ± 3.90	16.47 ± 2.65	0.0026
Drop in SBP 2 min After standing	20.67 ± 7.42	8.95 ± 6.01	<0.001

In our study the study population is divided in to TMT positive and TMT negative group. They are matched for age, BMI, mean duration of diabetes, percentage of CAN positivity, systemic

hypertension and menopause. There is no statistical difference is noted between these two groups in age, BMI , mean duration of diabetes, systemic hypertension and menopause. In all these parameters compared between these two groups the ‘p’ value is more than 0.05 which is statistically insignificant .But for cardiac autonomic neuropathy between these two groups the ‘p’ value is <0.001.This value is statistically significant and it shows the strong association of cardiac autonomic neuropathy in the TMT positive group.

TMT parameters like exercise duration in minutes,% of target heart rate and work done in METs are compared between TMT POSITIVE and TMT NEGATIVE groups. In this, exercise done in minutes between these two groups show statistically significant ‘p’ value (0.016). This shows the poor exercise capacity in the TMT positive groups.

While comparing both groups for heart rate variation to deep breathing, heart rate increase 15 sec after standing and drop in SBP 2 min after standing , the ‘p’ values are 0.0027,0.0026 and<0.001respectively. This shows the strong association of cardiac autonomic neuropathy in TMT POSITIVE group.

Important observations noted are

1. There was strong association of cardiac autonomic neuropathy in the TMT positive group.

2. Poor exercise capacity was noted in the TMT positive group.

CHARTS

Fig1. Age distribution

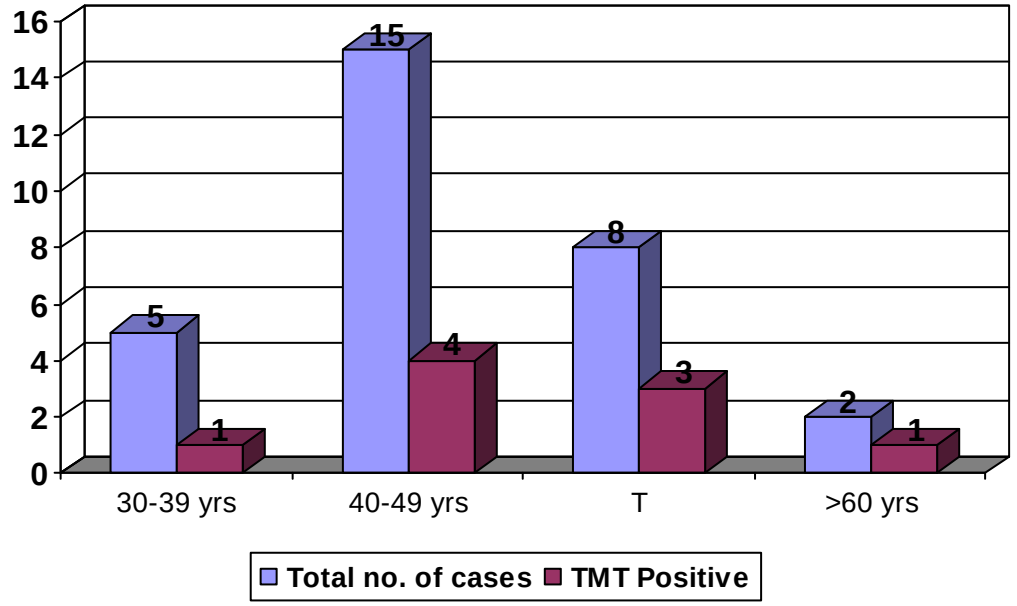


Fig.2 Age wise TMT positivity

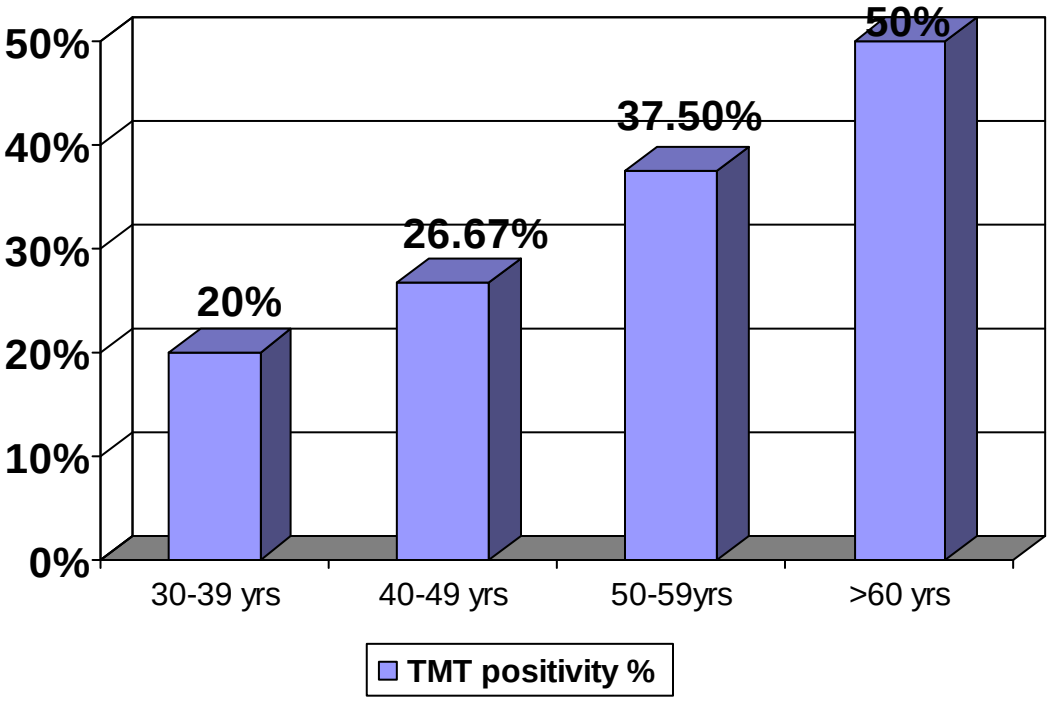


Fig.3 TMT Positivity

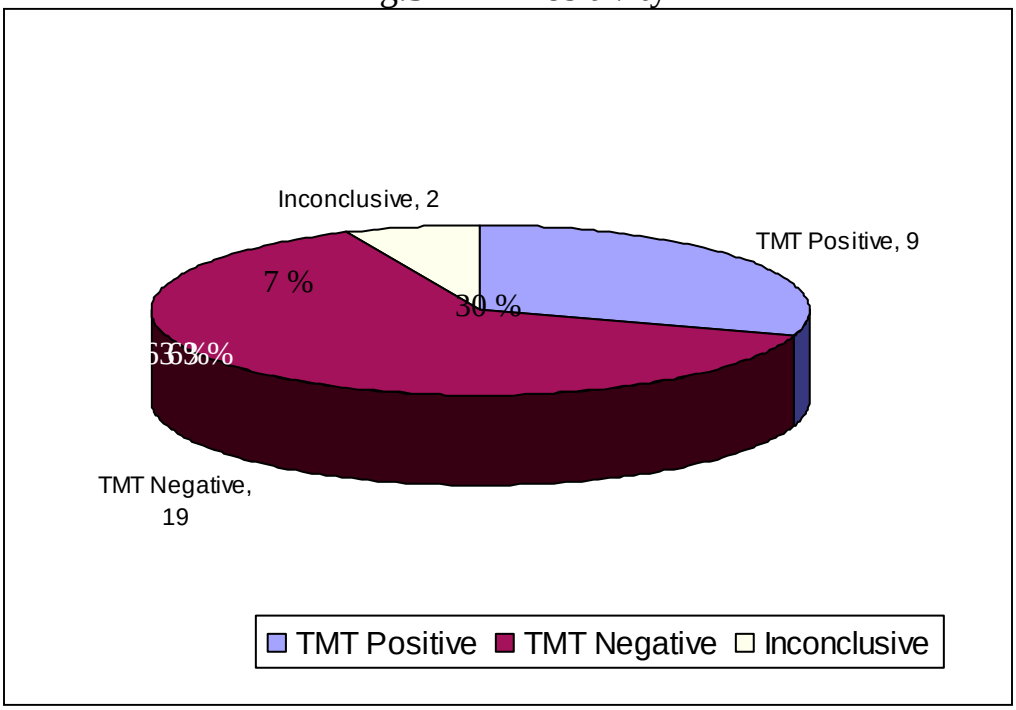


Fig.4 Duration of diabetes and TMT positivity

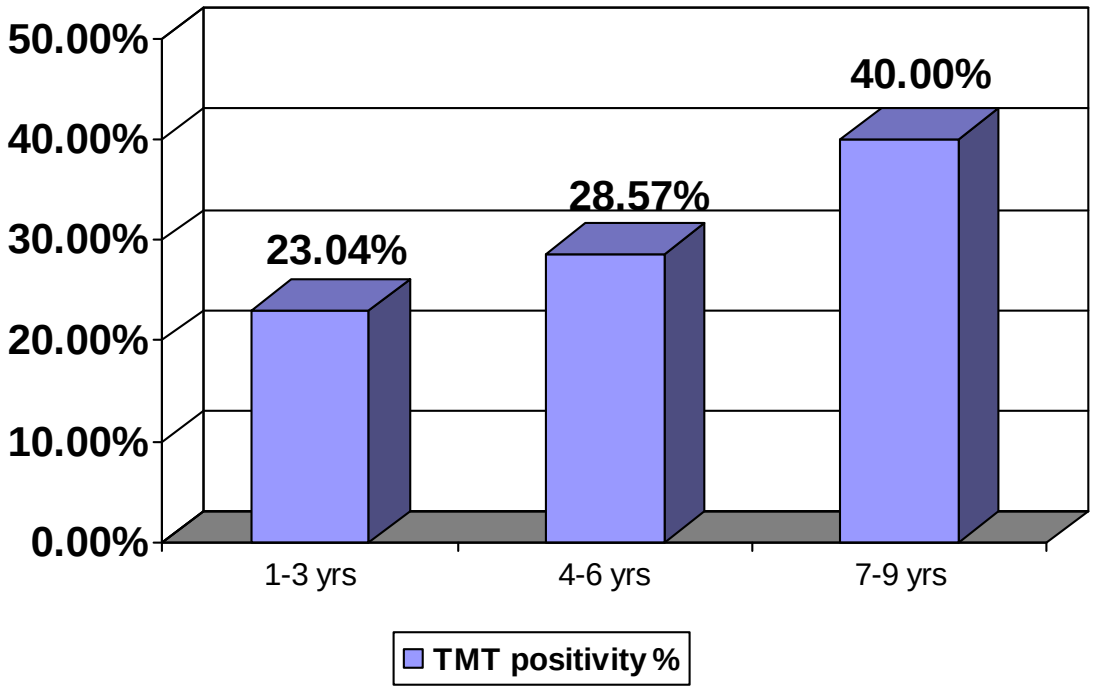


Fig.5 TMT positivity in Hypertensives

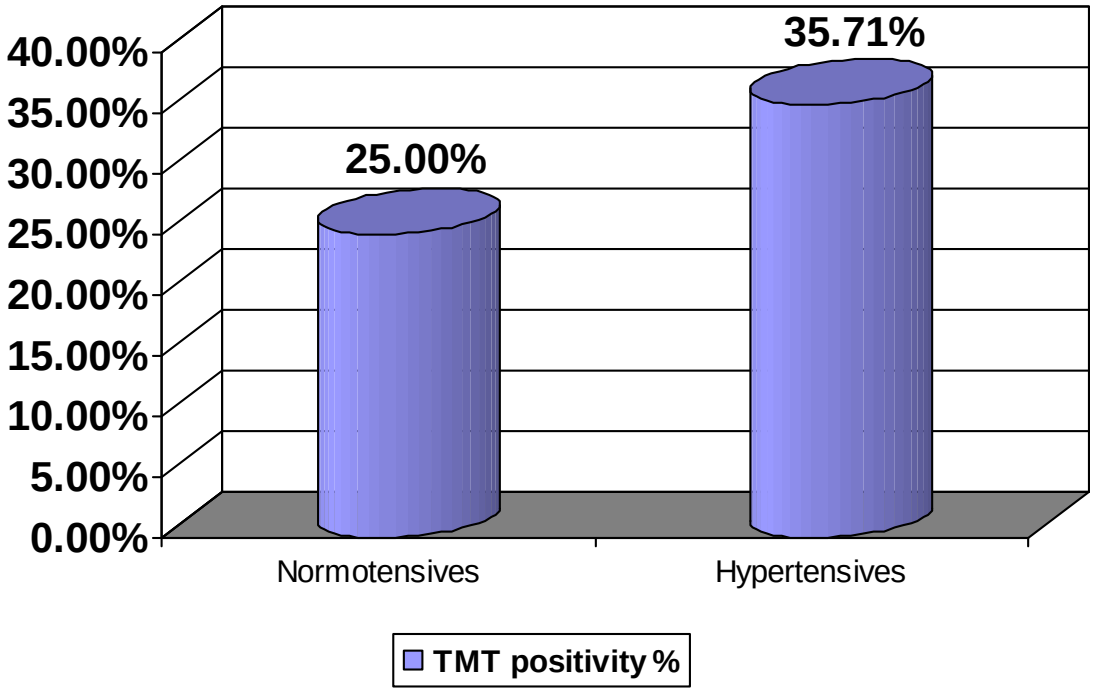


Fig.6 TMT positivity in Post menopausal women

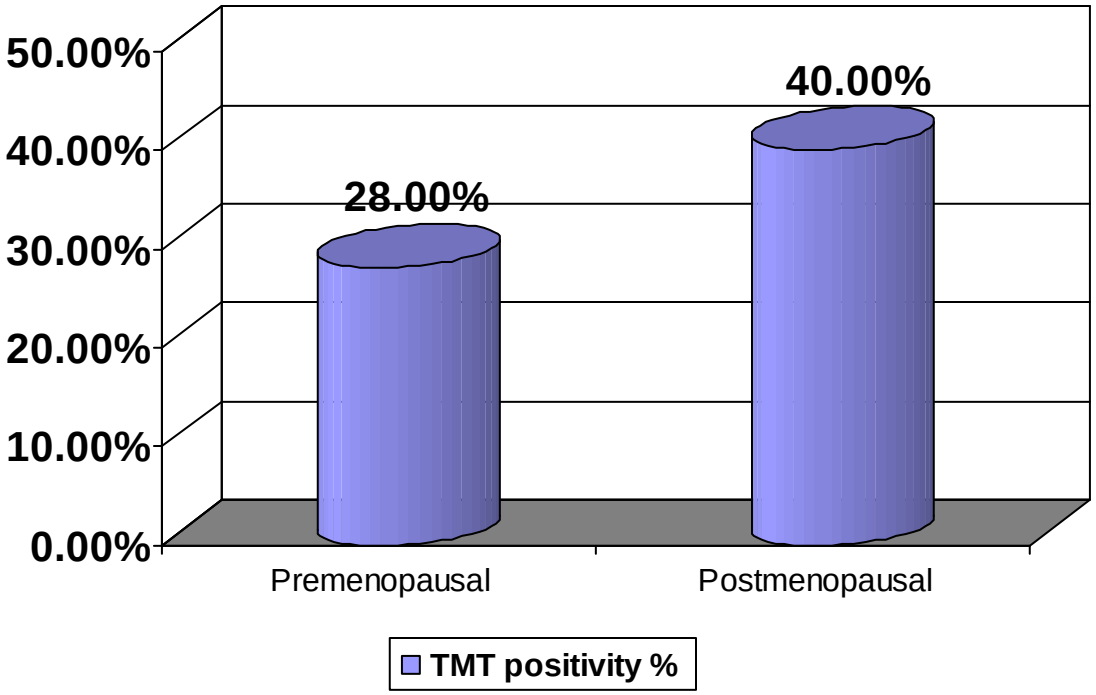


Fig.7 Obesity and TMT positivity

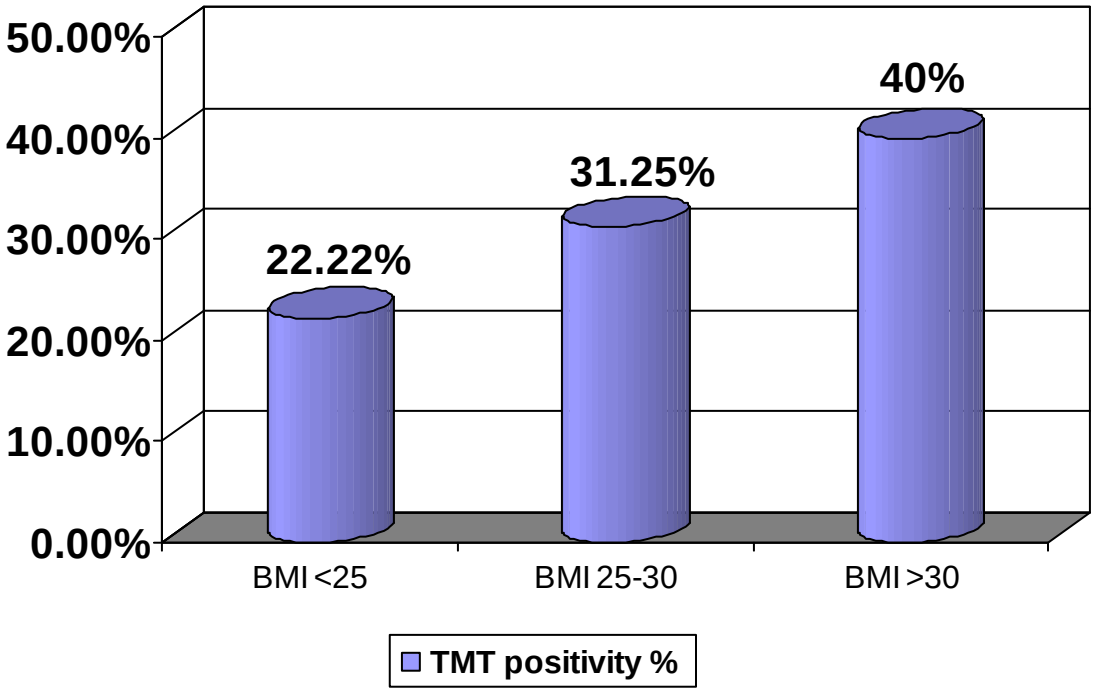


Fig.8 Cardiac Autonomic Neuropathy – prevalence in diabetes

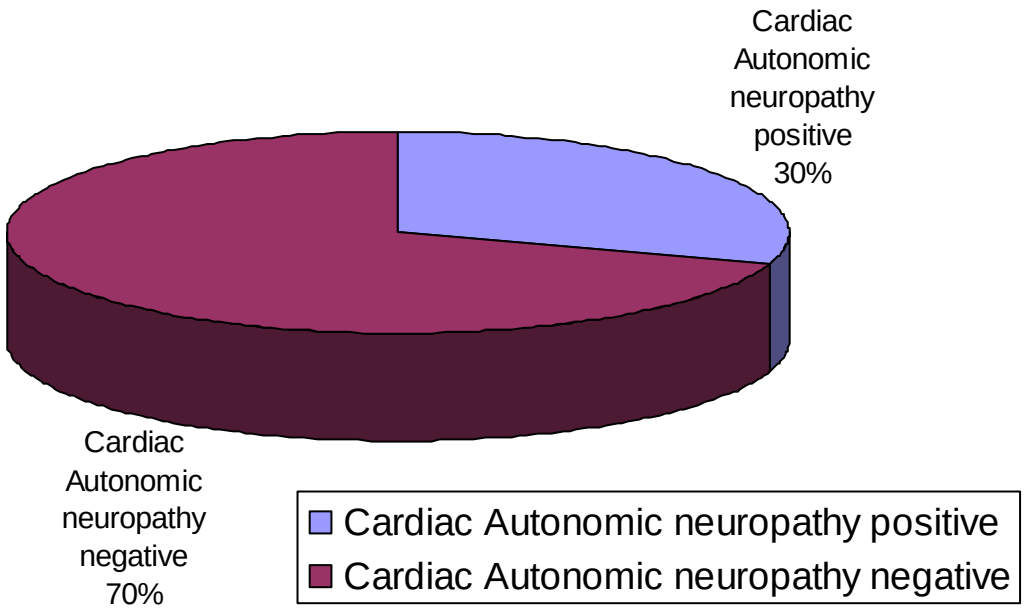


Fig.9 TMT positivity in cardiac autonomic neuropathy patients

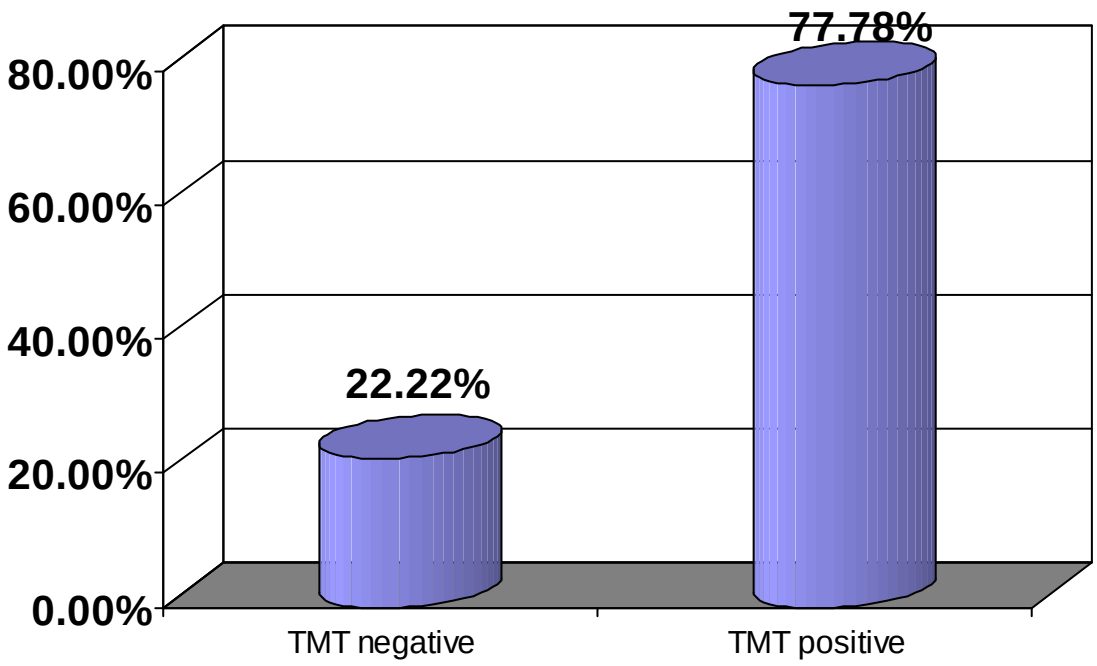


Fig.1

0 CAN positivity in TMT positive patients

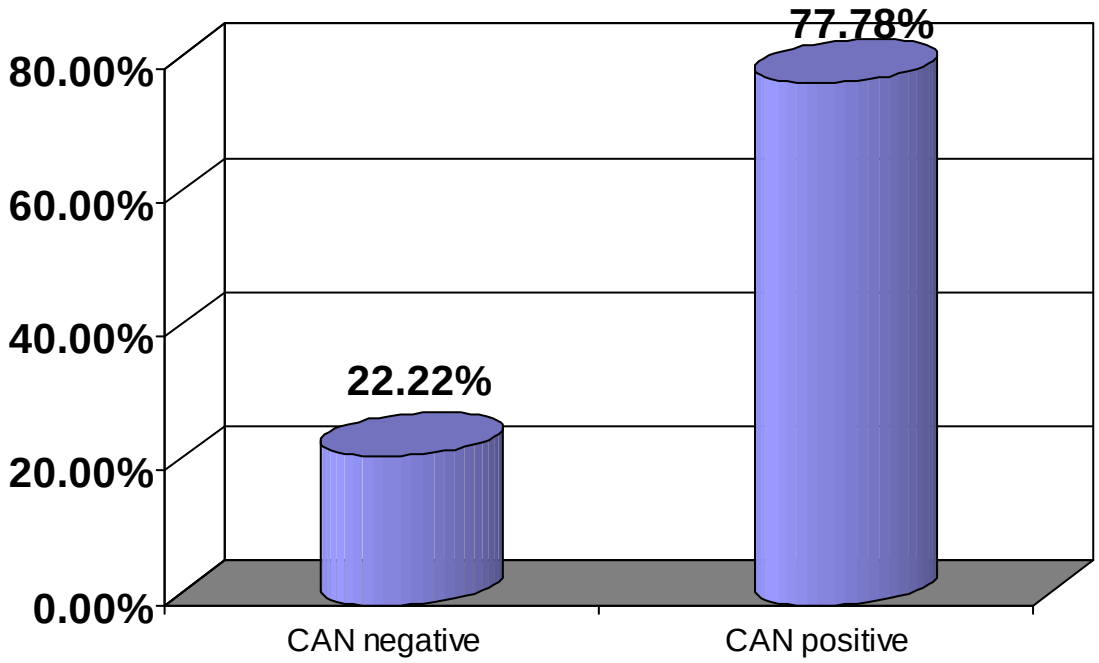
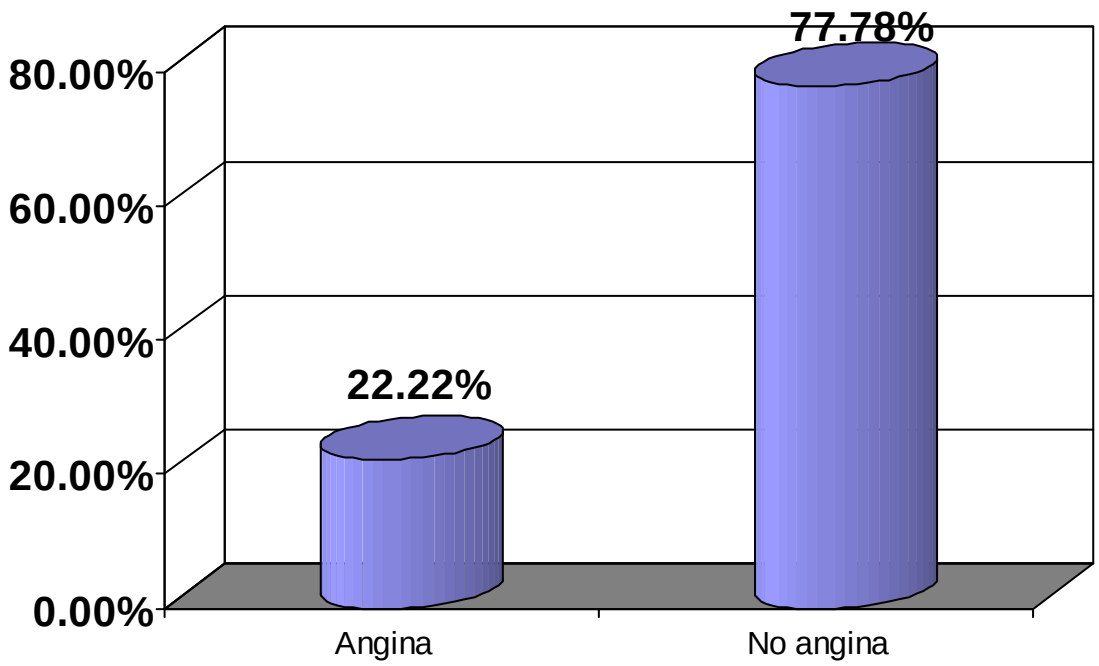


Fig.11 Prevalence of angina in CAN positive patients



DISCUSSION

In our study the prevalence of asymptomatic ischemic heart disease is found to be 30%. In various other international studies the prevalence of asymptomatic IHD in diabetes varies between 10-77%. Indian studies done by Shah et al and Banerjee et al show the prevalence of 36% any 35% respectively.

In one study conducted in Dept of cardiology, central railway head quarter hospital, Byculla, Bombay the prevalence of TMT positivity is 38% and autonomic neuropathy in tread mill positive patients was 72.2%. In our study in which female diabetics are the target population the TMT positivity was slightly lower (30%).

Cardiac autonomic neuropathy in TMT positive patients in our study is 77.78%. This almost matched the study done at (C.R.H.S.) Bombay. In the tread mill negative group the CAN positivity rate is 22.22%.[6]

In various analysis the CAN prevalence in diabetic population varies from 5 to 90% with the average of 30%.[1] In our study the prevalence of cardiac autonomic neuropathy is 30% which exactly matches the international studies.

In our study cardiac autonomic neuropathy is positive in 7 out of 9 TMT positive cases. This shows the strong relationship of the cardiac autonomic neuropathy with the silent myocardial ischemia.

CONCLUSION

1. The prevalence of asymptomatic ischemic heart disease was higher in diabetic women when compared to non diabetics. About one third of diabetic women are having asymptomatic ischemic heart disease which can be detected by simple treadmill test.

2. Prevalence of cardiac autonomic neuropathy was higher in treadmill positive patients who are otherwise asymptomatic. This shows that there is significant association between silent myocardial ischemia and cardiac autonomic neuropathy in diabetic population.

3. Poor exercise capacity was noted in the TMT positive but otherwise asymptomatic diabetic women.

SCOPE FOR FUTURE STUDY

1. In cardiac autonomic neuropathy positive diabetic patients, the incidence of ventricular arrhythmias are common. So this causes poor prognosis in cardiac autonomic neuropathy positive diabetics when they develop acute myocardial infarction. This aspect needs detailed analysis in future.

2. In all our patients we noticed poor glycemic control. In future studies, reversibility of cardiac autonomic neuropathy with the tight glycemic control can be studied. This may be useful to the clinician treating the diabetic patients.

3. Studies are also needed to check whether drugs used for the other diabetic microvascular complication can reverse the cardiac autonomic neuropathy.

4. Since insulin therapy exacerbates postural hypotension the incidence of autonomic neuropathy in them needs separate detailed analysis.

PROFORMA

Name	Age	Sex	OP no
Occupation	Height	Weight	B M I

Waist hip ratio

DIABETIC HISTORY

DURATION	SKIN	POLYURIA
POLYDIPSIA	POLYPHAGIA	LEG ULCERS
WEIGHT LOSS	CATARACT	

TREATMENT- (INSULIN/OHA)

IHD DATA

CHEST DISCOMFORT

ANGINA / NON ANGINAL
SUBSTERNAL/CRUSHING/SQUEEZING
FATIGUE,PALPITATION,DYSPNEA,DIAPHORESIS
GIDDINESS,NAUSEA,DYSPEPSIA,VOMITING

RISK FACTORS
- HYPERLIPEDEMIA
- OBESITY
- SMOKING/ALCOHOL

PAST HISTORY
- STD
- TUERCULOSIS/ATT
- BRONCHIAL ASTHMA
- RHD
- SEIZURES/STROKE
- DRUG INTAKE

FAMILY HISTORY

ISCHEMIC HEART DISEASE
SYSTEMIC HYPERTENSION
DIABETES

GENRAL EXAMINATION

PULSE RATE/RHYTHM/CHARACTER/VOLUME
COND OF VESSELWALL/PERIPHERAL PULSES/RADIO
FEMORAL DELAY
BLOOD PRESSURE
TEMPERATURE
RESP RATE
SWEATING/DYSPNEA/CYANOSIS
ANEMIA
JAUNDICE/CLUBBING/LYMPH NODE/
BOILS/FURUNCLES/FOOT ULCERS
XANTHALESMA/XANTHOMAS
THYROID DISORDERS

CARDIO VASCULAR SYSTEM
JVP
APICAL IMPULSE
PARASTERNAL HEEVE
PALPABLE SOUNDS
THRILL
PRECORDIAL PULSATIONS
AUSCULTATION
HEART SOUNDS
MURMURS
GALLOP

OTHER SYSTEMS

INVESTIGATIONS

URINE-ALBUMIN SUGAR ACETONE
BLOOD SUGAR-RANDOM FASTING PP
UREA CREATININE
LIPID PROFILE

SGOT
CXR PA VIEW
ECG
ECHOCARDIOGRAPHY

EXCLUSION CRITERIA

PATIENTS WITH PERIPHERAL VASCULAR DISEASE AS EVIDENCED BY ABSENT PH. PULSES
TYPE-1 DIABETES
KNOWN CASE OF CAD
SIGNS OF LVF
UN CONTROLLED SHT
HIGH RISK UNSTABLE ANGINA
OTHER ABSOLUTE CONTRA INDICATION FOR EXERCISE TESTING
AGE > 65 YEARS

TREADMILL TEST

CO EXISTING FACTORS
SYSTEMIC HYPERTENSION
MENOPAUSAL STATUS
MAXIMUM INCIDENCE BETWEEN WHAT AGE
DURATION OF DM WITH IHD
OBESITY WITH IHD
HYPERCHOLESTEROLEMIA WITH IHD
CONTROL OF DIABETES

S.No	Name	Age	Ht	Wt	BMI	BSA	DURn	ECG	ECHO	Exer time	METS	THR	Max HR	%
1	Beena	42	155	65	27.06	1.64	3	n	n	6.58	10.1	178	143	80.3
2	Suseela	54	150	60	26.67	1.54	9	T↓ V3-V6	n	6.27	10.1	166	128	77.1
3	Jayalaxmi	40	150	47	20.89	1.39	2	n	n	9.09	13.5	180	155	86.1
4	Chandrakala	54	150	50	22.22	1.43	6	n	n	7.39	10.1	166	165	99.4
5	Manjala devi	35	150	55	24.44	1.49	1	n	n	12.27	17.3	185	160	86.5
6	Gowri	45	150	55	24.44	1.49	5	n	n	9.08	13.5	175	154	88.0
7	Kala	49	155	60	24.97	1.58	7	n	n	6.5	10.1	171	126	73.7
8	Navaneetham	45	163	68	25.59	1.73	3	n	n	6.17	10.1	175	154	88.0
9	Saraswathi	32	158	65	26.04	1.66	1	n	n	7.44	10.1	188	163	86.7
10	Sarala	46	150	60	26.67	1.54	6	n	n	8	10.1	174	188	108.0
11	Padmavathy	37	150	62	27.56	1.56	2	n	n	8.01	10.1	183	169	92.3
12	Samundeshwari	55	150	65	28.89	1.6	7	n	n	9.27	13.5	165	133	80.6
13	Vijayakumari	47	155	70	29.14	1.69	4	n	n	7.34	10.1	173	140	80.9
14	Uma	45	155	70	29.14	1.69	5	n	n	5.31	7.1	175	172	98.3
15	Kasturi	40	145	75	35.67	1.66	1	T↓ V4-V6	n	9.05	13.5	180	184	102.2
16	Janaki	52	150	50	22.22	1.43	8	n	n	6.24	10.1	168	163	97.0
17	Kamala	60	150	55	24.44	1.49	9	n	n	8.03	10.1	160	160	100.0
18	Jeyakumari	41	145	56	26.63	1.46	1	T↓ V1-V5	n	8.56	10.1	179	195	108.9
19	Srikala	36	160	93	36.33	1.95	2	n	n	1.39	4.7	184	147	79.9
20	Rajalaxmi	55	150	60	26.67	1.54	9	n	n	6	7.1	166	146	88.0
21	Muthammal	45	160	80	31.25	1.83	3	n	n	6.06	10.1	175	138	78.9
22	Vijayalaxmi	49	150	50	22.22	1.43	5	n	n	6.45	10.1	171	172	100.6
23	Jayalaxmi	59	160	65	25.39	1.67	9	n	n	7.24	10.1	161	157	97.5
24	Surya	47	150	55	24.44	1.49	3	T↓ V1-V6	n	3.51	7.1	173	167	96.5
25	Parvathi	55	160	65	25.39	1.67	9	n	n	8.43	13.5	161	148	91.9
26	Prabha	50	150	60	26.67	1.54	1	n	n	4.32	7.1	170	157	92.4
27	Usha rani	46	150	65	28.89	1.6	9	n	n	7.49	10.1	174	181	104.0
28	Beula	62	160	80	31.25	1.83	9	n	n	4.52	7.1	158	133	84.2
29	Poongavanam	35	155	65	27.06	1.64	2	T↓ V4-V6	n	4.38	7.1	185	136	73.5
30	Mumtaz Begam	45	140	69	35.20	1.47	5	n	n	3.21	7.1	175	145	82.9

Master chart

S.No	Name	Age	TMT result	Auto NP	Chest pain	SHT	Menopause	HR variation to deep breathing	HR increase 15 sec after standing	Fall in SBP 2 min after standingn	CAN History
1	Beena	42	inconclusive	negative	No	No	No	21	19	6	No
2	Suseela	54	inconclusive	negative	Yes	Yes	No	25	17	8	No
3	Jayalaxmi	40	negative	negative	No	Yes	No	25	18	8	No
4	Chandrakala	54	negative	negative	No	No	No	22	18	6	No
5	Manjala devi	35	negative	negative	No	No	No	23	17	8	No
6	Gowri	45	negative	negative	No	No	No	23	17	6	No
7	Kala	49	negative	negative	No	Yes	No	26	18	8	No
8	Navaneetham	45	negative	negative	No	Yes	No	18	16	6	No
9	Saraswathi	32	negative	negative	No	No	No	26	18	8	No
10	Sarala	46	negative	negative	No	No	No	18	17	10	No
11	Padmavathy	37	negative	negative	No	No	No	20	16	6	No
12	Samundeshwari	55	negative	negative	No	Yes	Yes	24	19	8	No
13	Vijayakumari	47	negative	negative	No	No	No	22	16	6	No
14	Uma	45	negative	negative	No	No	No	23	18	8	No
15	Kasturi	40	negative	negative	No	No	No	19	19	8	No
16	Janaki	52	negative	negative	Yes	Yes	No	24	16	6	No
17	Kamala	60	negative	negative	Yes	No	Yes	18	18	6	No
18	Jeyakumari	41	negative	negative	Yes	No	No	21	17	6	No
19	Srikala	36	negative	negative	Yes	Yes	No	17	16	6	No
20	Rajalaxmi	55	negative	positive	No	Yes	Yes	6	9	30	Yes
21	Muthammal	45	negative	positive	No	Yes	No	8	10	20	Yes
22	Vijayalaxmi	49	positive	negative	Yes	No	No	27	19	8	No
23	Jayalaxmi	59	positive	negative	Yes	Yes	Yes	22	19	8	No
24	Surya	47	positive	positive	No	No	No	8	11	28	Yes
25	Parvathi	55	positive	positive	No	No	No	7	10	24	Yes
26	Prabha	50	positive	positive	No	Yes	No	8	10	26	Yes
27	Usha rani	46	positive	positive	No	Yes	No	9	11	24	Yes
28	Beula	62	positive	positive	No	Yes	Yes	9	9	22	Yes
29	Poongavanam	35	positive	positive	Yes	No	No	9	10	22	Yes
30	Mumtaz Begam	45	positive	positive	Yes	Yes	No	6	11	24	Yes

ABBREVIATIONS

CAN	– Cardiac autonomic neuropathy
CAD	– Coronary artery disease
CHD	– Coronary heart disease
MI	– Myocardial infarction
TMT	– Treadmill test
THR	– Target heart rate
SHT	– Systemic hypertension
SBP	– Systolic blood pressure
DBP	– Diastolic blood pressure
METS	– Metabolic equivalents
T2DM	– Type 2 Diabetes mellitus
BSA	– body surface area
HR	– Heart rate

BIBLIOGRAPHY

1. Braunwald's Heart disease, 7th edition ELSEVIER Saunders

2. Textbook of Diabetes, John C Pickup & Gareth Williams, 3rd edition Blackwell Science

3. Hurst's Heart disease 11th edition

4. Aoron I Vinik et al Semi Neurol 23: 365-372 2003

5. Ewing DJ et al Br Med J 1978 jan 21; 1(6106): 145-7

6. Gupta SB et al, Indian Heart J 1992 Jul-Aug; 44(4): 227-9 Silent myocardial and cardiac neuropathy n diabetics.

7. Duchen LW et al Ann Intern Med 1980 Feb;92(2 Pt 2): 301-3 Pathology of autonomic neuropathy in diabetes mellitus.

8. Harrison's Principles of Internal medicine, 16th edition McGraw Hill

9. Gibbons RJ, Balady GJ, Brick JT, et al: ACC/AHA 2002 guideline update for exercise testing summary article: A report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 40: 1531, 2002.

10. Fletcher GF, Balady GJ, Amsterdam EA, et al: Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association, Circulation 104:1694, 2001.

11. Balady GJ, Berra KA, Golding LA, et al: AGSM's Guidelines for Exercise Testing and Prescription, 6th Ed, Philadelphia, Lippincott Williams & Wilkins, 2000.

12. Wasserman K, Hansen JE, Sue DY, et al: Principles of Exercises Testing and Interpretation. 3rd Ed. Philadelphia. Lippincott Williams & Wilkins,1999.

13. American Thoracic Society/American College of Chest Physicians: Statement on Cardiopulmonary exercise testing. Am J Respir Crit Care Med 167: 211, 2003.

14. Hadeli KO, Siegel EM, Sherrill DL., et al: Predictors of oxygen desaturation during sub-maximal exercise in 8,000 patients. Chest120: 88, 2001.

15. Ellestad MH: Stress Testing: Principles and Practice, 4th Ed. Philadelphia, FA Davis,1996.

16. Froeliche VF, Myers J: Exercise and the Heart, 4th Ed. Philadelphia, W.B. Saunders, 2000.

17. Fletcher GF, Flipse TR, Kligfield P, et al: Current status of ECG stress testing. Curr Probl Cardiol 23: 353, 1998.

18. Fleg JL,Pina IL, Balady GJ, et al: Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association, Circulation 102: 1591, 2000.

19. Pollock ML, Franklin BA, Balady GJ et al: AHA Science Advisory. Resistance exercise in Individuals with an without cardiovascular disease: Benefits, Rationale, safety, and prescription. An advisory from the committee on exercise, Rehabilitation and prevention, council on clinical cardiology, American Heart

Association. Position paper endorsed by the American College of Sports Medicine, Circulation 101: 828, 2000.

20. Michaelides AP, Psomadaki ZD, Dilaveris PE et al: Improved detection of coronary artery disease by exercise electrocardiography with the use of right precordial leads. N Engl J Med 340:340, 1999.

21. Sabapathy R, Blloom HL, Lewis WR, Amsterdam EA: Right precordial and posterior chest leads do not increase detection of positiveresponse in electrocardiogram during exercise treadmill testing. Am J Cardiol 91: 75, 2003.

22. Rywik TM, Zink RC, Gittings NS, et al: Independent prognostic significance of ischemic ST Segment response limited to recovery from treadmill exercise in asymptomatic subjects. Circualtion 97:2117, 1998.

23. Sota JR, Watson DD, Beller GA: Incidence and significance of ischemic ST - segment depression occurring solely during recovery after exercise testing. Am J Cardiol88: 670, 2001.

24. Akutsu Y, Shinozuka A, Nishimuru H, et al: Significance of ST-segment morphology noted on electrocardiography during the recovery phase after exercise in patients with ischemic heart disease as analyzed with simultaneous dual-isotope single photon emission tomography. Am Heart J 144: 335, 2002.

25. Fearon WF, Leo DP, Froelicher VF: The effect of resting ST segment depression on the diagnostic characteristics of exercise treadmill testing. J Am Coll Cardiol 35: 1206, 2000.

26. Mobilia G, Zanco P, Desideri A, et al: T wave normalization in infarct-related electrocardiographic leads during exercise testing for detection of residual

viability: Comparison with position emission tomography. J Am Coll Cardiol 32:75, 1998.

27. Miwa K, Nakagawa K, Hirai T, Inoue H: Exercise-induced U-wave alterations as a marker of well-developed and well-functioning collateral vessels in patients with effort angina. J Am Coll Cardiol 35: 757, 2000.

28. Okin PM, Prineas RJ, Grandits G, et al: Heart rate adjustment of exercise induced ST segment depression identifies men who benefit from a risk factor reduction program. Circulation 96: 2899, 1997.

29. Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes 1997; 46 (Suppl. 2): 554-7.

30. Watkins P. The natural history of the dia5etic neuropathies. Q J Med 199O; 77:1209-18.

31. Wenger NK: Coronary heart disease and women: magnitude iii the problem. cardiol Rev 10:211, 2002.

32. Kennel WB: The Frarmingham Study: Historical insight on the impact cardiovascular risk factors in men versus women. J. Gend Specif Med 5:27, 2002.

33. Sullivan JL: Are menstruating women protected from heart disease because of, or ill spite of, estrogen? Relevance to the, iron hypothesis. Airs I loan J 145: 190, 2003.

34. Mikkola TS, Clarkson TB: Estrogen replacement therapy, atherosclerosis, and vascular function, Cardiovase Res 53: 605, 2002.

35. Mendelsohn ME: genomic and Nongenomic effects of estrogen in the vasculature. Am J cardiol 90: 3F, 2002.

36. Zanger D, Yang BK, Ardans J. et al: Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. J Am Coil Cardiol 36:1797, 2000.

37. Weinberg EO, Thienelt CD. Katz SE, et al: Gender differences in molecular remodeling in pressure overload hypertrophy. Jam CollCardiol 34: 264, 1999.

38. Andersen H. Motor function in diabetic neuropathy. Acta Neurol Scand 1999; 100: 211-20.

39. Dyck Pi, Lais A, Karnes it, O'Brien P, Rizza R. Fibre loss is primary and multifocal in sural nerves in diabetic polyrieuropathy. Ann Neural 1986; 19:425—39.

40. Brown MJ, Martin JR, Asbury AK. Painful diabetic neuropathy. A morphometric study. Arch Neural 1976; 33:164-71.

41. Said G, Slama G, Selva J. Progressive centripetal degeneration of axons in small fibre type diabetic polyneuropathy: a clinical arid pathological study. Brain 1983; 106:791-807.

42. Guy Clark CA, Malcolm PN, Watkins PJ. Evaluation of thermal and vibration sensation in diabetic neuropathy. Diobetologia 1985; 28: 131-8.

43. Boulton ,AJ, Ones FA, Jervell JA. Guidelines for the diagnosis and outptient management of diabetic peripheral neuro pathy. Diabet Med 1998; 15:508—14.

44. Mason J, O'Keefe C, McIntosh A etol. A systematic review of foot ulcer in patients with type 2 diabetes mellitus, 1: pre vention. Diabet Med 1999; 16: 801—12.

45. Watkins Pi, Edmonds ME. Sympathetic nerve failure in diabetes. Diabetologia 1983; 31:73-7.

46. Clarke SF, Ewing W, Campbell 1W. Diabetic autonomic neuropathy. Diabetologia 1979; 17:195-212.

47. Ewing Di, Martyn CN, Young RJ, Clarke SF. The value of cardio vascular autonomic function tests: 10 years' experience in diabetes. Diabetes Care 1985; 8:491-8.

48. Ewing DJ, Campbell 1W, Clarke SF. Mortality in diabetic auto nomicneuropathy. Loncet 1916; i: 601-3.

49. Berenson OS, Srinivasan SR. Bao W et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338:1650-6.

50. Krolewski AS, Kosinski EJ, Warram JH et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cordial 1987; 59: 750—5.

51. Krolewski AS, Czyzyk A, Janeczko D, Kopczynski J. Mortality from cardiovascular diseases among diabetics. Diabetologia 1977; 13: 345-50.

52. Kannel WB, McGee DL Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. Diabetes Care 1979; 2:120-6.

53. Barrett-Connor E, Wingard DL Sex differences in ischaemic heart disease mortality in diabetics: a prospective population based study. Am J Epidemiol 1983; 118: 489-96.

54. Schwartz. CJ. Valente AJ, Sprague FA. et al, Pathogenesis of the atherosclerotic lesion: Implications for diabetes mellitus. Diabetes Care 1992:15:1156—1167.

55. Stamler J, Vaccaro O. Neaton JD. Wentworth D. Diabetes, other risk factors and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care 1993:16: 434-444.

56. Gu K. Cowi CC. Harris Ml. Diabetes and decline in heart disease mortality in US adults. JAMA, 1999:1291-1297.

57. Kawate R, Yamakido M, Nishimoto Y. et al. Diabetes mellitus and its vascular complications in Japanese migrants on the island of Hawaii. Diabetes Care 1979: 2: 161-170.

58. Head J, Fuller ill. International Variations in mortality among diabetic patients: the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia 1990; 33: 447-481.

Patient ID : 254
First Name : MRS PRABHA
Birth Date : / /1956
Height : 150 cm
BSA : 1.54

Age : 50 Y
Weight : 60 kg
Target HR : 170

Gender : F

13:07:45

DEPARTMENT OF CARDIOLOGY
GOVERNMENT GENERAL HOSPITA
CHENNAI - 600 003.

Technician : NS
Code : PROF.SSS

Required by:
Indications : T2DM

Therapy :

	MAX VALUES		TIME
SPEED	4.0	Km/h	4:32
SLOPE	12.0	%	
	7.1	METS	
HR	157	bpm	4:33
	92.4	% Target HR	
RPP	264	mmHg*bpm/100	
BP	180	mmHg	5:10
ST+ (aVl)	1.3	mm	5:03
ST- (V5)	-2.7	mm	4:58

Protocol	Test	Stress	Recovery
Bruce	13:40	4:32	8:05

		DURATION	SPEED Km/h	SLOPE %	METS	HR bpm	BPs/BPd mmHg	STMax (V5)
Stand	01	0:33				94	140/ 80	-0.1
WarmUp	01	0:28	1.0	0.0	1.5	108	140/ 80	-0.2
Exe	01	3:00	2.7	10.0	4.7	146	160/ 80	-1.2
	Peak	1:32	4.0	12.0	7.1	155	160/ 80	-2.2
Recov	01	8:04	0.0	0.0	1.0	106	180/ 80	-1.1
Post	01	0:01	0.0	0.0	1.0	106	__/__	-0.9

Reasons for end : ST-T CHANGES,THR ACHIEVED.SIGNIFICANT

Symptoms : (NIL)

Conclusions : TARGET HEART RATE ACHIEVED.MODERATE EFFORT TOLERANCE.SIGNIFICANT ST-T CHANGES NOTED IN THE LATERAL LEADS FROM STAGE I ONWARDS PERSISTING UP TO 8TH MINUTE OF RECOVERY.TMT IS STRONGLY POSITIVE FOR INDUCIBLE ISCHAEMIA.

cardiac autonomic Neuropathy positive

3/2/08

Reported by : DR.G.RAVISHANKAR